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# Pd-catalysed intramolecular regioselective arylation of 2-pyrones, pyridones, coumarins and quinolones by C–H bond functionalization

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ABSTRACT

The intramolecular arylation of 2-pyrones, 2-pyridones, coumarins and quinolones is reported using $Pd^{II}$ precatalyst sources without added phosphine ligands. The excellent yields and convenient reagents enables the formation of various analogues containing these moieties, and access to potential biologically active candidates. Stoichiometric studies were carried out to provide an insight into the oxidation addition step. A switch in regioselectivity, together with a hydrodebromination process, was observed in the case of a 3-bromo-2-pyrone.



## 1. Introduction

The phenomenal abundance of the 2-pyrone moiety throughout plant, animal, microbial and insecticidal systems,[1] means that there is an ever-increasing emphasis on their synthesis.[2] The structural diversity of the 2-pyrone compounds can be readily seen in the wide array of naturally-occurring biologically active compounds. Examples include pyripyropene A,[3] and arisugacin A[4] (Fig. 1). Over 1300 of the closely-related coumarins have been identified from natural sources.[5] These compounds possess useful anti-tumour, anti-HIV and CNS-active properties.[6] Potential isosteres of 2-pyrones and 2-coumarins include 2-pyridones[7] and 2-quinolones.[8] Fusaricide, (Fig. 1) a tricyclic 2-pyridinone shows activity against *Candida albicans* and antiviral potential.[9] Tricyclic pyranoquinolones, e.g., Oricine,[10] have many applications in drugs, pharmaceuticals and agrochemicals.[11] Given the diverse structural features of biologically active 2-pyrones, pyridinones and related compounds, the development of efficient methods for their synthesis and functionalization is critical.

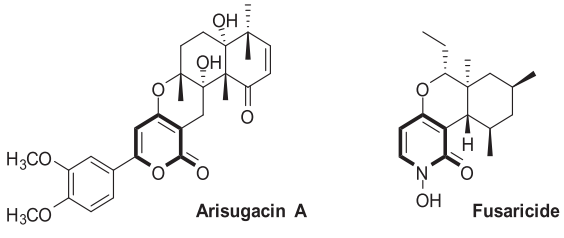


**Fig. 1.** Biologically-active polycyclic 6-aryl-2-pyrone and 2-pyridone natural products.

The formation of bicyclic 2-pyrone systems using a catalytic C–H functionalization strategy has been described by Fairlamb and Taylor.[12] They used systems involving $Pd^0$ precatalysts, additional phosphine ligands and $Cs_2CO_3$ as base in the formation of new five-membered rings using 4-phenoxypyrones. Regioselective cyclisation at the 3-position occurred, which mirrored the generally observed regioselectivity in the 6π-electrocyclisation/oxidative aromatisation reactions of related compounds.[13] We anticipated that a similar methodology could be used for the formation of six-membered rings using 4-benzyloxypyrones. It was anticipated that C3–H and C5–H functionalization could be possible. Surprisingly,

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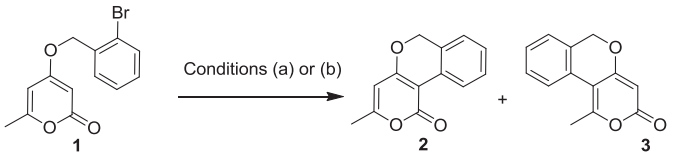
employment of the reported conditions[12,13] led to only trace quantities of cyclised product **2** (Scheme 1).




**Conditions (a):** $Pd(OAc)_2$ (cat.), TBAB, KOAc, DMF, 102 °C, 16 h
**Conditions (b):** $Pd_2dba_3$ (cat.), $PPh_3$, $Na_2CO_3$, NMP, 130 °C, 16 h

| Conditions | 2 | 3 |
|---|---|---|
| a | 45 | 11 |
| b | trace | - |

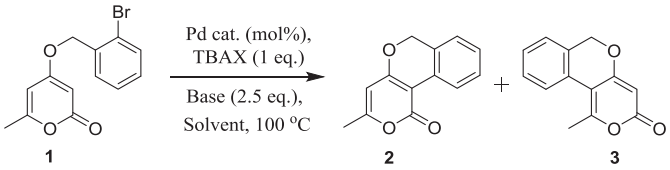
**Scheme 1.** Access to cyclised 2-pyrones **2** and **3**.

In this paper are reported alternative but complementary conditions[14] for the regioselective arylation of the 2-pyrone framework, using a simplified catalyst system[15] and 'Jeffrey's conditions' for the Mizoroki–Heck-type reaction.[16] Excellent yields were obtained at low Pd catalyst loading. The applicability of these conditions facilitates C–H bond functionalization of 2-pyrones, 2-coumarins, 2-pyridones and 2-quinolones. The mechanism for this process has also been investigated (experimentally and theoretically). Finally, a remarkable but unusual C5–H regioselective process, with concomitant hydrodebromination, was discovered as part of these studies.

## 2. Results and discussion

Conditions involving traditional Mizoroki–Heck-type and Jeffrey's conditions were evaluated initially (Scheme 1). While both sets of conditions gave the desired 3-cyclised product **2**, higher yields were obtained using a catalytic system involving added tetraalkylammonium salts, in the absence of intentionally-added phosphine. Furthermore, the 5-cyclised product **3** was found accessible (the X-ray crystallographic structures of **2** and **3** are shown in Fig. 2), unlike the previous report.[12]

**Table 1**
Optimisation studies[a]




| Entry | QAS (1 equiv) | Yield%[c] C(3):C(5)[c] |
|---|---|---|
| 1[b] | TBAB | 71:10 |
| 2[b] | TBAI | 14:0[d] |
| | **Base (2.5 equiv)** | **Yield% C(3):C(5)** |
| 3 | $Na_2CO_3$ | 58:6 |
| 4 | $Et_3N$ | 15:2[d] |
| | **Solvent** | **Yield% C(3):C(5)** |
| 5 | NMP | 52:7[d] |
| 6[b] | 1,4-Dioxane | 49:5 |
| 7 | Toluene | 60:4 |
| | **Pd cat. (mol %)** | **Yield% C(3):C(5)** |
| 8[b] | $Pd(OAc)_2$ (10) | 80:12 |
| 9 | $Pd(OAc)_2$ (5) | 60:4[d] |
| 10 | $Pd(OAc)_2$ (2) | 78:21 |

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol %), TBAB (1 equiv), KOAc (2.5 equiv), DMF, 100 °C, 16 h (unless otherwise specified within the table).
[b] 4(2-Iodobenzyloxy)-6-methyl-2-pyrone employed as starting material.
[c] Isolated product yield unless otherwise specified within the table.
[d] Yields determined by $^1H$ NMR spectroscopic analysis using an internal standard.

for this transformation. The organic base, triethylamine, also allowed for the formation of both regioisomers but in significantly reduced yields. Polar solvents gave lower yields compared to toluene, which was therefore used in subsequent reactions. Finally, evaluation of the catalytic loading was carried out (Table 2). It has been shown by Reetz and de Vries that reduced catalyst loading can improve reaction yields due to improved palladium nanoparticle solubilisation.[17] The catalyst loading was reduced to 5 mol % (~900 ppm Pd) and then 2 mol % (~360 ppm Pd), which led to an increase in yield along with a decrease in reaction times. Complete conversion of starting material provided the C-3 and C-5 arylated

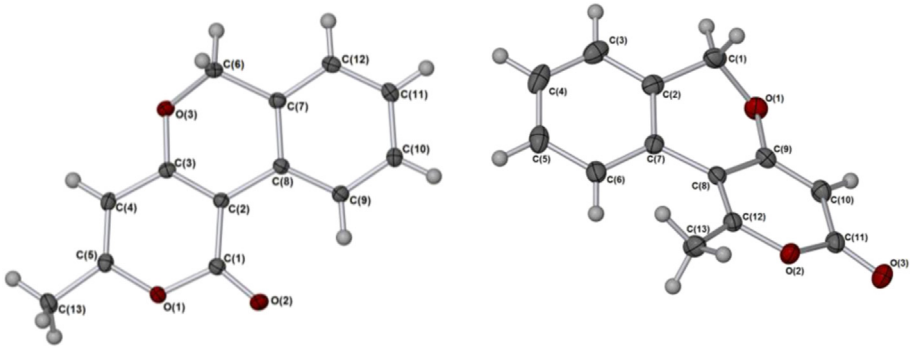



**Fig. 2.** Single crystal X-ray structures of regioisomers **2** (left) and **3** (right). Note: arbitrary atom numbering used, thermal ellipsoids shown at 50% (note: hydrogens are shown in these structures as grey spheres).

Initial conditions using $Pd(OAc)_2$ (10 mol %), TBAB (1 equiv), KOAc (2.5 equiv) and DMF promoted cyclisation at the 3- and 5-positions giving **2** and **3** in 45 and 11% yield, respectively. To probe the regioselectivity and improve upon the product yields, a series of reactions were performed by varying the anion of the quaternary ammonium salt (QAS), base, solvent and catalyst/catalytic loading (Table 1).

It was determined that TBAB is required and that all other halide anions gave poorer results. KOAc and $Na_2CO_3$ proved efficient bases

products in yields of 78% and 21%, respectively, using 2 mol % $Pd(OAc)_2$. The optimal reaction conditions were then applied to a variety of 4-(2-bromobenzyl)oxy substrates including 2-coumarin, 2-pyridinones and 2-quinolones and other 2-pyrone substrates. 6-Aryl-2-pyrones are ideal synthetic targets due to their wide natural occurrence and biological activity.[18]

To investigate the electronic effects of C-6 substitution, 2-pyrones **4a** and **4b** were synthesised using a methodology similar to that reported by Katritzky and co-workers.[19] Successful

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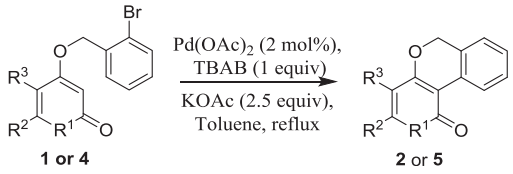
**Table 2**
Reactions using substituted substrates




**1 or 4** **2 or 5**

| Entry | Sub. | $R^1$ | $R^2$ | $R^3$ | Prod. | %Yield[a] C3:C5 |
|---|---|---|---|---|---|---|
| 1[b] | **1** | O | $CH_3$ | H | **2** | 80:12 |
| 2 | **1** | O | $CH_3$ | H | **2** | 78:21 |
| 3 | **4a** | O | Ph | H | **5a** | 99:<1 |
| 4 | **4b** | O | *p*-$CF_3(C_6H_4)$ | H | **5b** | 96:<1 |
| 5 | **4c** | O | 3,4,5-$(OMe)_3(C_6H_2)$–OMePh | H | **5c** | 64:<1 |
| 6 | **4d** | O | –$(CH)_4$– | — | **5d** | 62:<1 |
| 7 | **4e** | N–Me | $CH_3$ | H | **5e** | 85:<1 |
| 8 | **4f** | N–Bn | $CH_3$ | H | **5f** | 63:<1 |
| 9 | **4g** | N–Me | –$(CH)_4$– | — | **5g** | 65:<1 |

[a] Isolated product yield.
[b] Using 10 mol % $Pd(OAc)_2$.

intramolecular arylation was found possible, giving 2-pyrones **5a** and **5b** (Table 2, entries 3 and 4) in high yields (99% and 96%, respectively). 2-Pyrone **4c** allowed for successful intramolecular arylation to give **5c** in good yield (64%). Interestingly, in all of these substrates, regioselective arylation occurred exclusively at C3–H with no evidence of the C5 regioisomer, despite the presumed change in the acidity of the C5 proton. C–H acidity had been proposed as one factor in some C–H bond functionalization/DA reactions; with the more acidic sites being favoured for functionalization.[20] Gorelsky et al. have shown that the nucleophilicity of the arene (and C–H bond acidity) is a key factor in controlling the regioselectivity (note: the C3 position is considered the most nucleophilic site in 2-pyrones).[21] 2-Coumarin **4d** underwent intramolecular arylation in good yield (62%), with complete consumption of starting material noted after 1 h affording **5d**. Substituted tricyclic 2-pyridones are of interest as potential anti-Alzheimer's candidates.[22] Application of our optimised conditions to *N*-substituted pyridinones gave cyclised pyridinones **5e** and **5f**; no C-5 product could be isolated. The formation of these analogues required slightly longer reaction times (12 h), after which $Pd^0$ black was evident in the reaction vessel. *N*-methyl-2-quinolone **4g** also gave complete conversion to the C-3 cyclised quinolone **5g** in good yield, within 1 h.

To investigate whether the regioselectivity could be encouraged to occur solely at the C5 position, 'blocking' substituents were introduced at C3. Ideally, the substituent would either be easily removed, or useful in itself as a handle for further synthetic elaboration. We reasoned that a bromine atom could act as a potential chemical blocking-group with oxidative addition (and thus subsequent steps) favoured for the C–I bond (i.e., in a chemoselective-like process). This would allow for further decoration of the molecule via traditional cross-couplings, or by an alternative C–H bond functionalization strategy. Regiospecific bromination at the C3 position was performed, providing 3-bromo-2-pyrone **6** (Scheme 2). Intramolecular arylation employing our optimised arylation conditions afforded 2-pyrone **3** with no evidence of any C3 or C5 regioisomers **2** or **7**. Remarkably, C3 hydrodebromination had occurred to give **3**. The lack of any C3-cyclised regioisomer suggests that oxidative addition to the benzyl iodide occurred first, followed by C–H bond functionalization at C5. If hydrodebromination had occurred before intramolecular cyclisation, the system should have a free site for arylation at the C-3 position. This would allow for C–H bond functionalization to occur at both sides, presumably with a bias toward the C-3 position akin to our earlier work on **1** (Table 2). A methyl blocking-group was then introduced to give 2-pyrone compound **8**. Intramolecular arylation using our optimal conditions also led to regioselective C5 coupling, affording compound **9** in 98% yield (Scheme 2; see Fig. 3 for the X-ray crystallographic structure for **9**).

## 3. Mechanistic pathways

To gain an insight into the reaction mechanism of the $Pd(OAc)_2$/TBAB {reported herein, conditions (a)} and $Pd_2(dba)_3/PPh_3$[12] {conditions (b)} mediated reactions, experiments were conducted to deduce if oxidative addition to the aryl halide was feasible. We first attempted to improve the yield of the catalytic cyclization reaction outlined in Scheme 1, conditions (b), by employing iodide **10** (Scheme 3) in place of bromide **1**. However the yield of **2** could only be improved to 7% (cf. only trace product **2** was seen in Scheme 1 using bromide **1** under otherwise equivalent conditions). Thus we set out to isolate and test the oxidative addition product formed during these reactions to determine the susceptibility of this substrate to undergo oxidative addition. It was necessary to use phosphine for this purpose (phosphine is added to stabilize the oxidation addition product and allow its characterization using $^{31}P$ NMR spectroscopy). Reaction of $Pd^0{}_2(dba)_3$ with 2 equiv of $PPh_3$, in respect of $Pd^0$, gave $Pd^0(\eta^2\text{-dba})(PPh_3)_2$ **11**, as indicated by the presence of two $^{31}P$ NMR signals.[23] Addition of 3 equiv of **10** to **11**, under an $N_2$ atmosphere, resulted in 43% conversion to the oxidative addition product **12** *trans*-$[Pd^{II}I\{(C_7H_6O\text{-}2\text{-}(C_6H_5O_2)\}(PPh_3)_2)]$ (Scheme 3).[24] The oxidative addition product **12** (in a *trans*-geometry) was isolated and characterised (see Fig. 4 for X-ray structure of **12**).

The X-ray data denotes a distorted square planar *trans*-geometry with a torsion angle of −10.6 and +10.3, indicative of a slight bend out of the normal square planar orientation.[12] A single peak was observed in the $^{31}P$ NMR spectrum (22.7 ppm), characteristic of $Pd^{II}$ coordination. We found that 8 equiv of phosphine were necessary to afford **12**. When reduced amounts of $PPh_3$ were employed (less than 8 equiv), a 1:1 ratio of starting pyrone **10** and **12** precipitated from solution. This may be due to competing ligation of dba to the Pd complex. It has been shown that for displacement of dba to occur, higher phosphine equivalents may be necessary.[14a] Treatment of **12** with $Na_2CO_3$ (mimicking the Mizoroki–Heck type conditions (b) as per Scheme 1) in NMP at 130 °C showed near complete consumption of starting material (>95%). However, the crude mixture showed a number of side-products and the yield for **2** was determined to be 34% (by $^1H$ NMR spectroscopy using an internal standard). Thus it appears that 2-pyrone **10** is amenable to oxidative addition, but the process does not occur efficiently. The outcome provides an indication that the Mizoroki–Heck type conditions, requiring an *anti*-β-hydrogen elimination,[12] are problematic. Given the successful systems described above, we postulate that catalysis occurs via a more stable 16-electron $[Pd^0L_2X]^-$ intermediate[25] (where L is most likely solvent) derived from $Pd^0$ colloidal clusters stabilized by the tetraalkylammonium halides.[17b]

Finally, to gain insight into the origin of the regioselectivity in the reaction of **1**→**2**+**3**, DFT calculations (B3LYP) were conducted (Scheme 4). Here a Concerted-Metallation–Deprotonation (CMD)/Ambiphilic Metallation-Ligand Activation-6 (AMLA-6)[20b,26] mechanism was used as a model for C–H bond abstraction after the oxidative addition step. From the energy profile, the pathway leading to the C3 regioselectivity was calculated to be more favourable by 6.5 kcal/mol (in the free energy barrier). The proton-abstraction step is also easier at C3 (3.3 kcal/mol) than that a C5 (9.0 kcal/mol). Although the barrier for C5 is higher, it is still an accessible pathway. Further experimental and theoretical mechanistic studies are necessary, but these preliminary DFT calculations shed light on the experimentally observed regioselectivity.[27]

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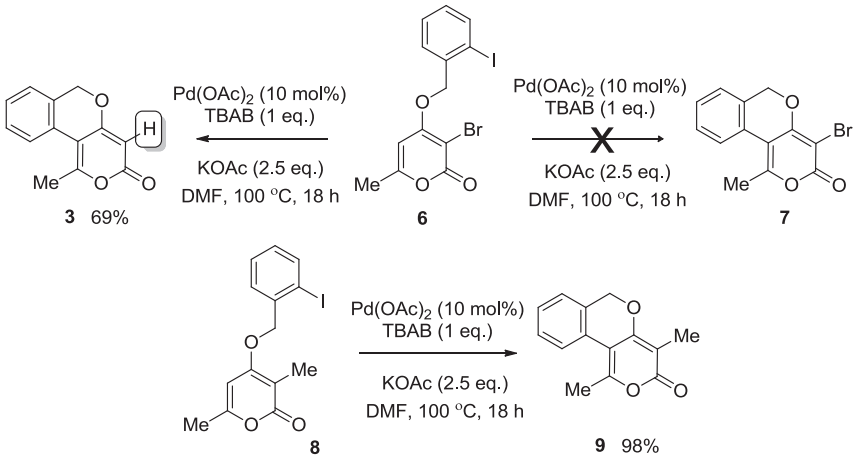



**Scheme 2.** Introduction of blocking substituents at C-3.

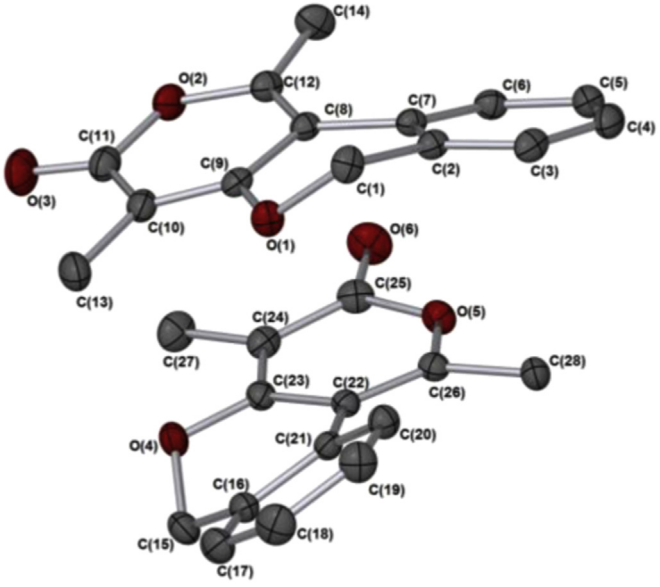


**Fig. 3.** Single crystal X-ray structure of **9**. Note: arbitrary atom numbering used, thermal ellipsoids shown at 50% and the hydrogens are omitted for clarity (two independent structures (conformers) are found in the asymmetric unit cell).

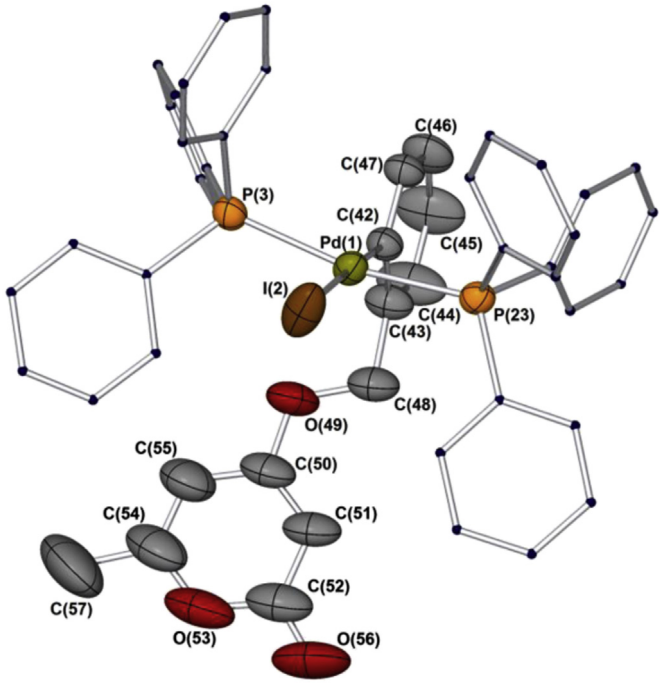
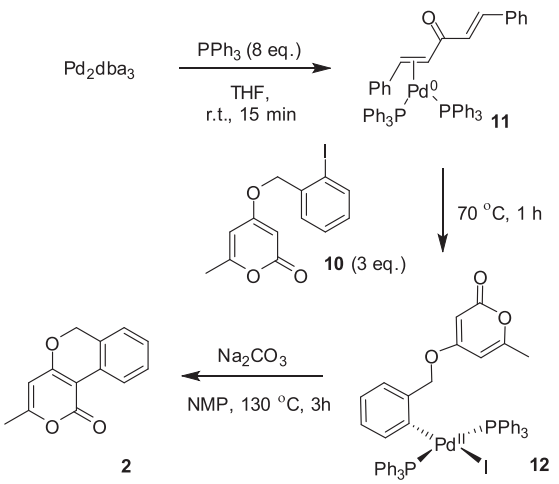


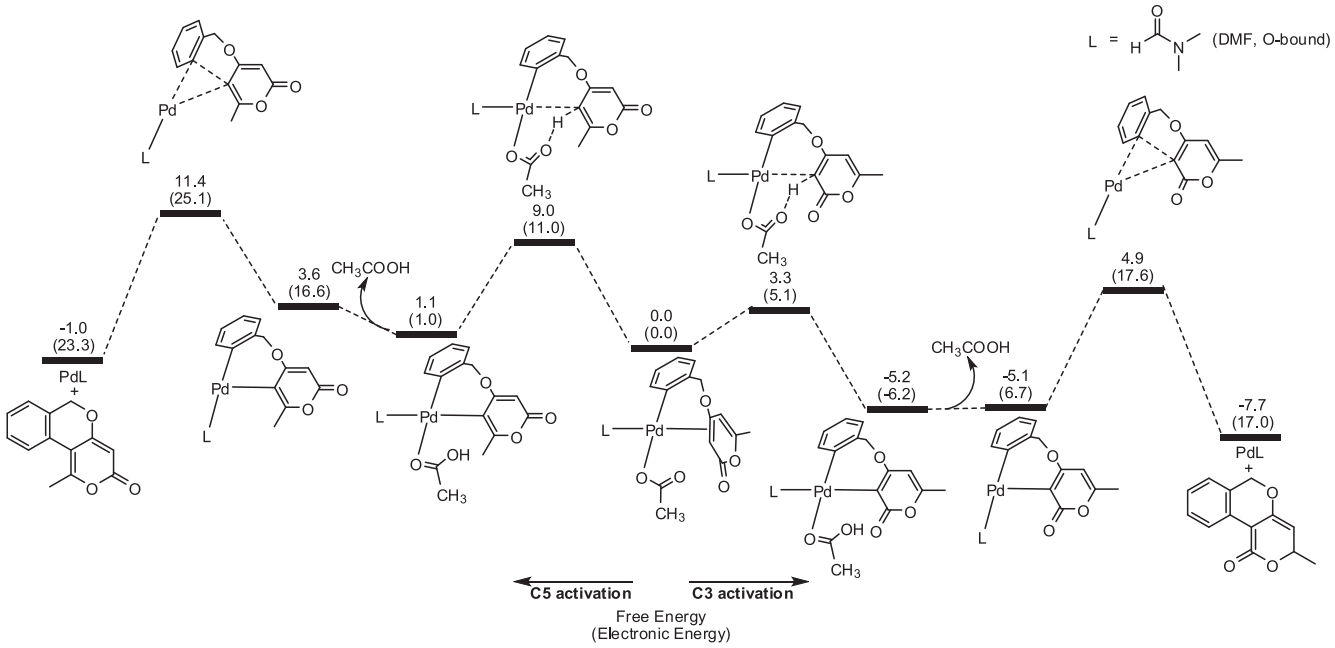
**Fig. 4.** Single crystal X-ray structure of **12**. Note: arbitrary atom numbering used, thermal ellipsoids shown at 50% (the phenyl group carbon atoms are shown as blue spheres and the hydrogens are omitted for clarity).




**Scheme 3.** Stoichiometric studies: isolation of oxidative addition product **12** and its reaction with $Na_2CO_3$ to give **2**.

## 4. Conclusion

In conclusion, two sets of catalytic conditions were tested in the Pd-catalysed cyclization of a number of biologically-relevant heterocyclic substrates. Using $Pd^0$ precatalyst sources with added phosphine ligands, poor conversion was achieved. Utilising Jeffery conditions at lower Pd catalyst loadings, excellent product yields were obtained. Optimized conditions using catalytic $Pd(OAc)_2$, TBAB and KOAc in toluene proved an effective route to substituted tricyclised 2-pyrones, 2-pyridinones, 2-coumarins and 2-quinolones. The excellent yields and convenient reagents enables the formation of analogues containing these moieties, and access to potential biologically-active candidates. The introduction of a bromine at the C-3 position of the 2-pyrone allowed access to the C5 cyclized product—a remarkable switch in regioselectivity. Stoichiometric studies showed that oxidative addition of '$Pd^0(PPh_3)_2$', derived from $Pd^0(\eta^2\text{-dba})(PPh_3)_2$, to **10** is viable (to give **12**), but




**Scheme 4.** Energy profile involving **2** and **3**—the origin of the regioselectivity, as determined by DFT calculations (B3LYP).

poor yields of the final product **2** and side-reactions were noted. This suggests that intermediates of the type $[Pd^0L_2X]^-$ (L=solvent), and possibly higher order Pd species, that can be formed under Jeffrey's conditions, are key to the success of the reaction conditions.

## 5. Experimental section

### 5.1. General procedures

Melting point determinations were performed by the open capillary method and are reported uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded at 25 °C in $CDCl_3$ at 300 and 75 MHz spectrometer unless otherwise specified, with TMS as the internal standard. Chemical Shifts ($\delta_H$, $\delta_C$ and $\delta_P$) were expressed as parts per million (ppm) positive shift being downfield from TMS; coupling constants ($J$) are expressed in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a TOF MS instrument with ESI source. High-resolution mass spectra were recorded only for new compounds. Literature citations are provided for known compounds and representative characterisation data. IR spectra were recorded on an FT-IR spectrometer as a thin film (liquid samples) or applied as a solution in chloroform, and the chloroform was allowed to evaporate (solid samples). Column chromatography was carried out using 60 Å (35–70 μm) silica.

### 5.2. General procedure for the preparation of 4-hydroxy-6-aryl-2*H*-pyran-2-one[19]

A round bottomed flask charged with the appropriate 2,2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-one (3 mmol, 1 equiv) and toluene (30 mL) was heated under reflux for 20–30 min. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate and hexanes mixture as an eluent to afford the pure title products.

*5.2.1. 4-Hydroxy-6-phenyl-2-pyrone*[19] (***18***). Yellow solid (0.198 g, 99%), mp 256–258 °C, (lit.[28] 254–256 °C); $\delta_H$ (DMSO-$d_6$, 300 MHz) 7.86–7.84 (2H, m), 7.54–751 (3H, m), 6.75 (1H, d, $J$=1.96), 5.38 (1H, d, $J$=1.94); $\delta_C$ (DMSO-$d_6$, 75.5 MHz) 170.5, 163.0, 160, 131.02, 130.9, 129, 125.4, 98.4, 89.6; $m/z$ ($ES^+$): 189 $[(M+H)^+]$.

*5.2.2. 4-Hydroxy-6-(4-(trifluoromethyl)phenyl)-2H-pyran-2-one* (***19***). Yellow solid (0.123 g, 96%), mp 268–269 °C; $\nu_{max}/cm^{-1}$ (KBr): 3096, 2611, 1726, 1679, 1658, 1634, 1576, 1479, 1322; $\delta_H$ (Acetone-$d_6$, 500 MHz) 8.12 (2H, d, $J$=8.2), 8.03 (2H, d, $J$=7.5), 6.84 (1H, d, $J$=1.7), 5.53 (1H, d, $J$=1.95); $\delta_C$ (Acetone-$d_6$, 75.5 MHz) 170.7, 163.5, 159.8, 136.2, 132.4 (q, $J$=33), 127.2, 126.8 (q, $J$=3.8), 125 (q, $J$=272), 100.5, 91.8; $m/z$ ($ES^+$): 256 $[(M+H)^+]$; HRMS (ESI-TOF): Exact mass calculated for $C_{12}H_8F_3O_3$ $[M+H^+]$, 257.0426. Found 257.0418.

*5.2.3. 4-Hydroxy-6-(3,4,5-trimethoxyphenyl)-2H-pyran-2-one* (***20***). Orange solid, mp 182–184 °C (lit. 185–188 °C[29]); $\delta_H$ (DMSO-$d_6$, 300 MHz) 12.0 (1H, br s), 7.12 (2H, s), 6.85 (1H, s), 5.39 (1H, s), 3.86 (6H, s), 3.72 (3H, s); $\delta_C$ (DMSO-$d_6$, 75.5 MHz) 171.2, 163.6, 160.4, 153.6, 126.9, 140.3, 103.5, 98.8, 89.7, 60.6, 56.6; $m/z$ ($ES^+$): 279 $[(M+H)^+]$.

*5.2.4. 4-Hydroxy-1,6-dimethylpyridin-2(1H)-one* (***21***). White solid (2.02 g, 40%), mp 233–234 °C (lit.[30] 232 °C); $\delta_H$ (DMSO-$d_6$, 300 MHz) 10.27 (1H, br s), 5.75 (1H, dd, $J$=2.6, 0.7), 5.48 (1H, d, $J$=2.6), 3.3 (3H, s), 2.26 (3H, s); $\delta_C$ (DMSO-$d_6$, 75.5 MHz) 165.4, 163.9, 147.8, 99.6, 95.5, 29.62, 20.28; $m/z$ ($ES^+$): 140 $[(M+H)^+]$.

*5.2.5. 1-Benzyl-4-hydroxy-6-methylpyridin-2(1H)-one*[31] (***22***). White solid (0.566 g, 33%), mp 212–213 °C (lit.[32] 208–210 °C); $\delta_H$ (DMSO-$d_6$, 300 MHz) 10.5 (1H, br s), 7.35–7.28 (2H, m), 7.26–7.21 (1H, m), 7.09 (2H, d, $J$=7.14), 5.79 (1H, dd, $J$=2,5, 0.6), 5.59 (1H, d, $J$=2.6), 5.18 (2H, s), 2.16 (3H, s); $\delta_C$ (DMSO-$d_6$, 75.5 MHz) 165.9, 163.4, 147.6, 137.7, 128.5, 126.8, 126.1, 100.4, 95.8, 45.2, 19.9; $m/z$ ($ES^+$): 216 $[(M+H)^+]$.

### 5.3. General procedure for preparation of (4-(2-halobenzyl) oxy)-substrates[14d]

To a 3-necked round bottomed flask were added the appropriate 4-hydroxy-6-substituted-2*H*-substrate (1 equiv), 2-halobenzyl bromide (1.2 equiv), anhydrous potassium carbonate (7.2 equiv) and dry acetone. The resulting reaction mixture was then stirred under reflux at 79 °C for 4 h. The reaction mixture was allowed to

cool and filtered. The solid was washed with acetone (2×20 mL). The washes were combined and the solvent was concentrated under reduced pressure. The residual mass was dissolved in $CH_2Cl_2$ (2×50 mL) and washed with water (1×20 mL). The combined organic extracts was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate and hexanes mixture as an eluent to afford the pure title products.

*5.3.1. 4-((2-Bromobenzyl)oxy)-6-methyl-2H-pyran-2-one (**1**).* White solid (1.26 g, 63%), mp 99 °C (lit.[14d] 135–137 °C); $\nu_{max}/cm^{-1}$ (KBr): 3435, 1723, 1567, 1379, 1248, 755; $\delta_H$ (300 MHz) 7.61 (1H, dd, *J*=7.92, 1.15), 7.43–7.33 (2×1H, 2×overlapping dt, *J*=7.67, 1.4), 7.27–7.21 (1H, m), 5.87 (1H, m), 5.51 (1H, d, *J*=2.19), 5.08 (2H, s), 2.3 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 167.0, 164.8, 162.4, 133.8, 133.0, 130.2, 129.3, 127.8, 123.0, 100.4, 88.7, 70.0, 19.9; *m/z* ($ES^+$): 297, $Br^{81}$ [(M+H)$^+$], 296, $Br^{79}$ [(M+H)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{13}H_{11}O_3Br$ [M+H$^+$], 294.9977. Found 294.9977.

*5.3.2. 4-((2-Iodobenzyl)oxy)-6-methyl-2H-pyran-2-one (**10**).* White crystals (0.23 g, 65%), mp 101–103 °C; (Found C, 45.60; H, 3.44. $C_{13}H_{11}O_3I$ requires C, 45.63; H, 3.24%); $\nu_{max}/cm^{-1}$ (KBr): 1722, 1648, 1563, 1417, 1356, 1242, 1142, 1004, 758; $\delta_H$ (300 MHz) 7.88 (1H, d, *J*=7.8), 7.4–7.38 (2H, m), 7.1–7.05 (1H, m), 5.88 (1H, m), 5.51 (1H, d, *J*=2.2), 5.01 (2H, s), 2.23 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 170, 164.8, 162.4, 136.7, 139.7, 130.4, 129.0, 128.6, 100.4, 97.9, 88.8, 74.4, 19.9; *m/z* ($ES^+$): 343 [(M+H)$^+$ 100%]; HRMS (ESI-TOF): Exact mass calculated for $C_{13}H_{11}O_3I$ [M+H$^+$], 342.9841. Found 342.9828.

*5.3.3. 4-((2-Bromobenzyl)oxy)-6-phenyl-2H-pyran-2-one (**4a**).* Yellow solid (0.087 g, 31%), mp 134 °C; $\nu_{max}/cm^{-1}$ (KBr): 3431, 3102, 2923, 2854, 1711, 1639, 1571, 1557, 1426; $\delta_H$ (300 MHz) 7.84–7.80 (2H, m), 7.63 (1H, dd, *J*=8, 1.08), 7.48–7.44 (4H, m), 7.37 (1H, dd, *J*=7.5, 1.1), 7.28–7.24 (1H, m), 6.54 (1H, d, *J*=2.16), 5.65 (1H, d, *J*=2.13), 5.16 (2H, s); $\delta_C$ ($CDCl_3$, 125.75 MHz) 170.0, 164.0, 160.5, 133.8, 133.1, 131.1, 130.3, 130, 129.4, 128.9, 127.8, 125.7, 123.03, 97.6, 89.8, 70.3; *m/z* ($ES^+$): 359, $Br^{81}$ [(M+H)$^+$], 357, $Br^{79}$ [(M+H)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{18}H_{14}O_3Br$ [M+H$^+$], 357.0126. Found 357.0109.

*5.3.4. 4-((2-Bromobenzyl)oxy)-6-(4-(trifluoromethyl)phenyl)-2H-pyran-2-one (**4b**).* Yellow solid (0.062 g, 30%), mp 172–173 °C; $\nu_{max}/cm^{-1}$ (KBr): 3424, 3094, 2924, 2854, 1714, 1647, 1574, 1557, 1451, 1434, 1410, 1329; $\delta_H$ (300 MHz) 7.93 (2H, d, *J*=8.2), 7.72 (2H, d, *J*=8.3), 7.6 (1H, dd, *J*=7.9, 1.2), 7.47 (1H, dd, *J*=7.6, 1.6), 7.38 (1H, td, *J*=7.5, 1.2), 7.29–7.24 (1H, m), 6.59 (1H, d, *J*=2), 5.7 (1H, d, *J*=2.1), 5.17 (2H, s); $\delta_C$ ($CDCl_3$, 125.75 MHz) 169.6, 163.4, 134.3, 133.6, 133.1, 132.5 (q, *J*=32.8), 130.4, 129.5, 127.8, 126.02, 125.9 (q, *J*=3.8), 123.7 (q, *J*=272), 123.14, 99.5, 90.7, 70.5; *m/z* ($ES^+$): 427, $Br^{81}$ [(M+H)$^+$], 425, $Br^{79}$ [(M+H)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{19}H_{13}BrF_3O_3$ [M+H$^+$], 425.0002. Found 424.9995.

*5.3.5. 4-((2-Iodobenzyl)oxy)-6-(3,4,5-trimethoxyphenyl)-2H-pyran-2-one (**4c**).* Cream solid (0.09 g, 35%), mp 177–179 °C; $\nu_{max}/cm^{-1}$ (NaCl): 3055, 2987, 2686, 2410, 2306, 1719, 1633, 1585, 1503, 1266, 1132, 749; $\delta_H$ (300 MHz) 7.91 (1H, dd, *J*=7.8, 0.9), 7.47–7.38 (2H, m), 7.09 (1H, td, *J*=7.4, 2.1), 7.03 (2H, s), 6.46 (1H, d, *J*=2.1), 5.64 (1H, d, *J*=2.1), 5.09 (2H, s), 3.91 (6H, s), 3.9 (3H, s); $\delta_C$ ($CDCl_3$, 125.75 MHz) 169.9, 164.0, 160.3, 153.5, 140.8, 139.8, 136.7, 130.5, 129.2, 128.6, 126.4, 103.1, 97.9, 97.6, 89.5, 74.7, 61.0, 56.4; *m/z* ($ES^+$): 495 [(M+H)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{21}H_{20}O_6I$ [M+H$^+$], 495.0305. Found 495.0299.

*5.3.6. 4-((2-Bromobenzyl)oxy)-1,6-dimethylpyridin-2(1H)-one (**4e**).* White solid (0.421 g, 19%), mp 187–188 °C (lit.[26] 134–135 °C); $\delta_H$ (300 MHz) 7.59 (1H, dd, *J*=7.92, 1.2), 7.44 (1H, dt, *J*=7.7, 0.7), 7.33 (1H, td, *J*=7.5, 1.2), 7.2 (1H, td, *J*=7.8, 1.7), 5.93 (1H, d, *J*=2.7), 5.88 (1H, dd, *J*=2.7, 0.8), 5.05 (2H, s), 3.47 (3H, s), 2.32 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 165.9, 165.3, 146.4, 134.9, 132.8, 129.6, 128.9, 127.6, 122.6, 100.78, 95.8, 69.7, 30.6, 20.92; *m/z* ($ES^+$): 308, $Br^{79}$ [(M+H)$^+$], 310, $Br^{81}$ [(M+H)$^+$].

*5.3.7. 1-Benzyl-4-((2-bromobenzyl)oxy)-6-methylpyridin-2(1H)-one (**4f**).* White solid (0.455 g, 51%), mp 116–117 °C; (Found: C, 62.35; H, 4.26; N, 3.46. $C_{20}H_{18}BrNO_2$ requires C, 62.51; H, 4.72; N, 3.65); $\nu_{max}/cm^{-1}$ (KBr): 3053, 2916, 1659, 1624, 1597, 1563, 1440, 1354; $\delta_H$ (300 MHz) 7.59 (1H, dd, *J*=8, 1.12), 7.47 (1H, dd, *J*=7.7, 1.5), 7.37–7.29 (3H, m), 7.26–7.19 (3H, m), 7.15 (2H, d, *J*=7.2), 6.02 (1H, d, *J*=2.7), 5.88 (1H, dd, *J*=2.7, 0.7), 5.08 (2H, s), 2.23 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 166.2, 165.3, 146.7, 136.8, 134.9, 132.9, 129.7, 129.1, 128.8, 127.6, 127.3, 126.4, 122.7, 101.4, 96, 69.4, 46.6, 20.6; *m/z* ($ES^+$): 384, $Br^{79}$ [(M+H)$^+$], 386, $Br^{81}$ [(M+H)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{20}H_{19}BrNO_2$ [M+H$^+$], 384.0599. Found 384.0570.

*5.3.8. 4-((2-Bromobenzyl)oxy)-2H-chromen-2-one (**4d**).* White crystals (0.281 g, 22%), mp 152–154 °C (lit.[33] 142 °C); $\delta_H$ (300 MHz) 7.89 (1H, dd, *J*=7.8, 1.3), 7.65 (1H, dd, *J*=7.9, 1.1), 7.60–7.51 (2H, m), 7.42–7.28 (4H, m), 5.8 (1H, s), 5.28 (2H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 165.1, 162.8, 153.4, 133.7, 133.2, 132.6, 130.4, 129.3, 127.7, 124.0, 123.2, 123.1, 116.9, 91.5, 70.5; *m/z* ($ES^+$): 332 [(M+H)$^+$].

*5.3.9. 4-((2-Bromobenzyl)oxy)-1-methylquinolin-2(1H)-one (**4g**).* White solid (0.234 g, 24%), mp 163–164 °C (lit.[33] 156–158 °C), $\delta_H$ (300 MHz) 8.07 (1H, dd, *J*=8.01, 1.47), 7.64–7.54 (3H, m), 7.39–7.34 (2H, m), 7.27–7.21 (2H, m), 6.14 (1H, s), 5.24 (2H, s), 3.68 (s, 3H); $\delta_C$ ($CDCl_3$, 75.5 MHz) 163.7, 161.3, 139.8, 134.7, 132.9, 131.4, 129.9, 128.9, 127.7, 123.5, 122.8, 121.8, 116.4, 114.1, 97.9, 69.9, 29.2; *m/z* ($ES^+$): 345, $Br^{79}$ [(M+H)$^+$], 347, $Br^{81}$ [(M+H)$^+$].

### 5.4. Preparation of 3-substituted-4(2-iodobenzyloxy)-6-methyl-2*H*-pyran-2-one

*5.4.1. 3-Bromo-4(2-iodobenzyloxy)-6-methyl-2H-pyran-2-one (**6**).* 4-(2-Iodobenzyloxy)-6-methyl-2-pyrone **10** (0.367 g, 1.07 mmol) was dissolved in dichloromethane (3 mL, 0.33 M), in a round-bottomed flask wrapped in aluminium foil. The reaction was stirred at room temperature (17 °C) and a solution of bromine (0.188 g, 1.18 mmol) in dichloromethane (3 mL, 0.33 M) was added dropwise over the period of 1 h. The reaction mixture was concentrated under reduced pressure and the solid residue recrystallised from ethanol to afford the title product as a white crystalline solid (0.311 g, 69%), mp 210–215 °C; $\nu_{max}/cm^{-1}$ ($CH_2Cl_2$): 2960, 1719, 1641, 1533, 1315, 1063, 1010; $\delta_H$ (400 MHz) 7.87 (1H, dd, *J*=8.0, 1.0), 7.51 (1H, dd, *J*=8.0, 1.0), 7.43 (1H, td, *J*=7.5, 1.0), 7.09 (1H, td, *J*=7.5, 2.0), 6.02 (1H, app. d, *J*=1.0), 5.20 (2H, s), 2.28 (3H, d, *J*=1.0); $\delta_C$ ($CDCl_3$, 101 MHz) 165.8, 163.0, 161.0, 139.6, 136.8, 130.4, 129.0, 128.4, 96.3, 96.1, 89.7, 75.5, 20.5; *m/z* ($ESI^+$) 421, $Br^{79}$ [(M+H)$^+$], 423, $Br^{81}$ [(M+H)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{13}H_{10}BrINaO_3$ [M+H$^+$], 442.8751. Found 442.8762.

*5.4.2. 3,6-Dimethyl-4(2-iodobenzyloxy)-2H-pyran-2-one (**8**).* A mixture of 3,6-dimethyl-4-hydroxy-2-pyrone (0.350 g, 2.5 mmol), 2-iodobenzylbromide (0.825 g, 2.78 mmol) and anhydrous potassium carbonate (0.518 g, 5.94 mmol) were stirred under reflux in dry acetone (10 mL, 0.25 M) for 16 h. The reaction mixture was allowed to cool to room temperature, and then quenched with water (20 mL) and ethyl acetate (20 mL) and the layers separated. The product formed as a white precipitate formed upon quenching and was separated by filtration through a sintered glass funnel and washed with cold EtOAc. The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The solid residue was washed through a sintered glass funnel

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using cold EtOAc and water to afford the title product as a white powder (0.329 g, 37%), mp 185–189 °C; $\nu_{max}/cm^{-1}$ (DMSO): 2903.7, 1691, 1573, 1307, 1245, 1127; $\delta_H$ (400 MHz, DMSO-$d_6$) 7.94 (1H, d, $J$=7.5), 7.54 (1H, dd, $J$=7.5, 1.8), 7.46 (1H, t, $J$=7.0), 7.16 (1H, t, $J$=7.0), 6.62 (1H, s), 5.18 (2H, s), 2.24 (3H, s), 1.78 (3H, s); $\delta_C$ (DMSO-$d_6$, 101 MHz) 165.2, 164.5, 160.9, 139.4, 137.9, 130.6, 130.1, 128.6, 99.5, 99.3, 96.2, 74.2, 19.7, 8.7; $m/z$ (ESI+) 378.9783 [(M+Na)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{14}H_{14}IO_3$ [M+H$^+$], 356.9982. Found 356.9982.

### 5.5. General procedure for preparation of the intramolecular coupled products

To a dried sealed Schlenk tube, the appropriate (4-(2-halobenzyl)oxy)-substrate (1 equiv), TBAB (1.2 equiv), $Pd(OAc)_2$ (2 mol %), KOAc (2.5 equiv) and 2 mL of toluene were added. Nitrogen gas was bubbled through the reaction mass. The reaction was heated to 127 °C and reaction progress to completion was monitored by TLC analysis. The reaction mass was cooled to room temperature and diluted with water (15 mL), and extracted with EtOAc (3×15 mL). The combined organic extracts was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate and hexanes mixture as an eluent to afford the pure title products.

*5.5.1. 3-Methylpyrano[4,3-c]isochromen-1(6H)-one (**2**).* White solid (0.057 g, 78%), mp 139–141 °C (lit.[14d] 110–113 °C); $\delta_H$ (300 MHz) 8.46 (1H, dd, $J$=7.9, 0.75), 7.39–7.33 (1H, m), 7.24–7.29 (1H, m), 7.04 (1H, dd, $J$=7.4, 0.7), 5.91 (1H, d, $J$=0.8), 5.23 (2H, s), 2.26 (3H, d, $J$=0.8); $\delta_C$ ($CDCl_3$, 75.5 MHz) 166.3, 162.5, 161.7, 128.9, 127.5, 126.8, 126.5, 124.0, 123.8, 100.3, 99.8, 69.3, 20.1; $m/z$ (ES$^+$): 215 [(M+H)$^+$].

*5.5.2. 1-Methylpyrano[4,3-c]isochromen-3(6H)-one (**3**).* Off-white solid (0.015 g, 21%), mp 143 °C; $\nu_{max}/cm^{-1}$ (KBr): 1725, 1557, 1407, 1229, 1196, 1006; $\delta_H$ (300 MHz) 7.51–7.40 (2H, m), 7.34 (1H, td, $J$=7.4, 1.5), 7.23 (1H, dd, $J$=7.4, 0.6), 5.76 (1H, s), 5.06 (2H, s), 2.65 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 168.9, 163.6, 159.7, 131.4, 128.9, 127.7, 126.1, 125.6, 125.3, 93.5, 77.2, 69.4, 20.5; $m/z$ (ES$^+$): 215 [(M+H)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{13}H_{10}O_3$ [M+H$^+$], 215.0711. Found 215.0708.

*5.5.3. 3-Phenylpyrano[4,3-c]isochromen-1(6H)-one (**5a**).* Bright yellow solid (0.023 g, 99%), mp 137 °C; $\nu_{max}/cm^{-1}$ (KBr): 3445, 3060, 2924, 1074, 1627, 1544, 1496, 1417; $\delta_H$ (300 MHz) 8.53 (1H, dd, $J$=7.9, 0.75), 7.89–7.83 (2H, m), 7.49–7.45 (3H, m), 7.43–7.37 (1H, m), 7.28 (1H, td, $J$=7.45, 1.25), 7.07 (1H, dd, $J$=7.44, 0.7), 6.56 (1H, s), 5.29 (2H, s); $\delta_C$ ($CDCl_3$, 125.75 MHz) 166.1, 160.9, 160, 131.1, 130.9, 129.5, 128.4, 127.8, 127.1, 126.5, 125.7, 124.3, 123.8, 101.1, 97.6, 69.4; $m/z$ (ES$^+$): 277 [(M+H)$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{18}H_{13}O_3$ [M+H$^+$], 277.0865. Found 277.0852.

*5.5.4. 3-(4-(Trifluoromethyl)phenyl)pyrano[4,3-c]isochromen-1(6H)-one (**5b**).* Yellow solid (0.0396 g, 96%), mp 172–173 °C; $\nu_{max}/cm^{-1}$ (KBr): 3431, 2925, 2855, 1684, 1634, 1543, 1409, 1328; $\delta_H$ (300 MHz) 8.45 (1H, d, $J$=7.26), 7.9 (2H, d, $J$=8.2), 7.66 (2H, d, $J$=8.4), 7.34 (1H, td, $J$=7.7, 1.2), 7.23 (1H, td, $J$=7.5, 1.2), 7.02 (1H, d, $J$=7.11), 6.57 (1H, s), 5.25 (2H, s); $\delta_C$ ($CDCl_3$, 150 MHz) 165.6, 160.5, 158, 134.2, 132.6 (q, $J$=33), 129.1, 128.2, 127.1, 126.1, 126 (q, $J$=3), 125.9, 124.4, 123.9, 123.7 (q, $J$=270), 102.1, 99.1, 69.5; HRMS (ESI-TOF): Exact mass calculated for $C_{19}H_{12}F_3O_3$ [M+H$^+$], 345.0739. Found 345.0753.

*5.5.5. 3-(3,4,5-Trimethoxyphenyl)pyrano[4,3-c]isochromen-1(6H)-one (**5c**).* Yellow solid (0.014 g, 64%), mp 154–156 °C; $\nu_{max}/cm^{-1}$ (NaCl): 3055, 2987, 2686, 2306, 1712, 1549, 1504, 1422, 1265, 1133, 896, 743; $\delta_H$ (300 MHz) 8.52 (1H, dd, $J$=7.9, 0.7), 7.43–7.37 (1H, m), 7.28 (1H, overlapping td, $J$=7.5, 1.2), 7.09 (1H, overlapping m), 7.07 (2H, s), 6.49 (1H, s), 5.30 (2H, s), 3.94 (6H, s), 3.91 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 166.1, 160.9, 159.9, 153.6, 140.9, 129.0, 127.8, 127.1, 126.5, 126.3, 124.3, 123.8, 103.1, 100.8, 97.3, 69.5, 61.02, 56.4; $m/z$ (ES$^+$): 367 [M+H$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{21}H_{19}O_6$ [M+H$^+$], 367.1182. Found 367.1166.

*5.5.6. 2,3-Dimethyl-2,6-dihydro-1H-isochromeno[4,3-c]pyridin-1-one (**5e**).* White solid (0.031 g, 85%), mp 95–96 °C (lit.[18c] 100–102 °C); $\delta_H$ (300 MHz) 8.8 (1H, d, $J$=8), 7.36 (1H, td, $J$=8, 1.3), 7.22 (1H, td, $J$=7.44, 1.2), 7.05 (1H, dd, $J$=7.44, 0.64), 5.89 (1H, d, $J$=0.6), 5.11 (2H, s), 3.55 (3H, s), 2.35 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 162.6, 162.2, 146.2, 128.7, 128.5, 128.1, 126.7, 124.4, 123.6, 105.5, 100.2, 68.9, 29.7, 21.22; $m/z$ (ES$^+$): 228 [M+H$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{14}H_{13}NO_2$ [M+H$^+$], 228.1025. Found 228.1017.

*5.5.7. 2-Benzyl-3-methyl-2,6-dihydro-1H-isochromeno[4,3-c]pyridin-1-one (**5f**).* White solid (0.050 g, 63%), mp 126–127 °C; $\nu_{max}/cm^{-1}$ (KBr): 3420, 3075, 2958, 2923, 2854, 1745, 1636, 1602, 1579, 1554, 1487, 1425; $\delta_H$ (300 MHz) 8.83 (1H, d, $J$=8), 7.37–7.29 (3H, m), 7.24–7.18 (4H, m), 7.07 (1H, dd, $J$=7.44, 0.64), 5.89 (1H, s), 5.38 (2H, s), 5.15 (2H, s), 2.88 (3H, s); $\delta_C$ ($CDCl_3$, 125.75 MHz) 162.9, 162.2, 146.6, 136.8, 128.82, 128.7, 128.6, 128.1, 127.3, 126.9, 126.4, 124.5, 123.7, 105.8, 100.8, 69, 47, 20.9; $m/z$ (ES$^+$): 304 [M+H$^+$]; HRMS (ESI-TOF): Exact mass calculated for $C_{20}H_{18}NO_2$ [M+H$^+$], 304.1338. Found 304.1339.

*5.5.8. 6H, 11H-[2]Benzopyrano[4,3-c][1]benzopyran-11-one (**5d**).* White powdery solid (0.019 g, 62%), mp 136 °C (lit.[19] 137 °C); $\delta_H$ (300 MHz) 8.55 (1H, dd, $J$=7.9, 0.8), 7.87 (1H, dd, $J$=7.9, 1.4), 7.59–7.4 (1H, m), 7.44–7.38 (1H, m), 7.36–7.27 (3H, m), 7.13 (1H, dd, $J$=7.4, 0.7), 5.40 (2H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 161.2, 160.2, 152.9, 132.5, 129.1, 128.3, 127.4, 126.7, 124.9, 124.1, 124.0, 123.1, 116.5, 115.2, 102.7, 69.8; $m/z$ (ES$^+$): 251 [(M+H)$^+$].

*5.5.9. 12-Methyl-6H-isochromeno[4,3-c]quinolin-11(12H)-one (**5g**).* White solid (0.041 g, 65%), mp 131 °C (lit.[19] 130–132 °C); $\nu_{max}/cm^{-1}$ (KBr): 3432, 2925, 2855, 1630, 1589, 1487, 1466; $\delta_H$ (300 MHz) 8.8 (1H, d, $J$=7.36), 8.05 (1H, dd, $J$=8.01, 1.4), 7.63–7.57 (1H, m), 7.44–7.36 (2H, m), 7.33–7.23 (2H, m), 7.15 (1H, dd, $J$=7.4, 0.7), 5.21 (2H, s), 3.78 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz) 161.4, 158.0, 139.2, 131.4, 128.7, 128.7, 127.6, 125.3, 123.8, 123.5, 121.8, 115.6, 107.9, 69.4, 29.4; $m/z$ (ES$^+$): 264 [(M+H)$^+$].

*5.5.10. 1,4-Dimethyl-3H,6H-pyrano[4,3-c]isochromen-3-one (**9**).* Orange crystalline solid (0.049 g, 98%), mp 122–126 °C; $\nu_{max}/cm^{-1}$ ($CH_2Cl_2$): 2961, 1704, 1648, 1570, 1231, 1215, 1107, 1027; $\delta_H$ (300 MHz) 7.48 (1H, d, $J$=8.0), 7.42 (1H, td, $J$=7.5, 1.5), 7.33 (1H, td, $J$=7.5, 1.5), 7.24 (1H, d, $J$=8.0), 5.06 (2H, s), 2.62 (3H, s), 2.01 (3H, s); $\delta_C$ ($CDCl_3$, 101 MHz) 165.0, 163.7, 156.2, 131.9, 128.8, 127.6, 127.0, 125.3, 107.7, 102.6, 69.5, 20.2, 8.9; HRMS (ESI-TOF) calcd for $C_{14}H_{13}O_3$ [M+H$^+$], 229.0859. Found 229.0858.

### 5.6. *trans*-[Pd{($C_7H_6O$-2-($C_6H_5O_2$))}I($PPh_3$)$_2$] (12)

To a dried sealed Schlenk tube, $Pd_2dba_3$ (26.8 mg, 29.31 μmol) and $PPh_3$ (61.5 mg, 234.5 μmol) and 8 mL of THF were added. Nitrogen gas was bubbled through the reaction mass and the reaction was stirred at ambient temperature for 15 min followed by the addition of **10** (30 mg, 87.94 μmol). The solution was then allowed to stir for 1 h at 70 °C. The THF was then concentrated under reduced pressure to afford a yellow resin, which was subsequently dissolved in $Et_2O$ (5 mL) and stored between 8 and 5 °C for 12 h, affording yellow crystals. The solution was then filtered and the crystals washed with $Et_2O$ (2 mL), and dried under high vacuum to

afford the pure title produced as a yellow crystalline solid (0.0368 g, 43%), $\delta_H$ (300 MHz) 7.47–7.43 (13H, m), 7.33 (7H, t, $J$=7.4), 7.25–7.21 (10H, m), 6.82 (1H, dd, $J$=7.7, 0.9), 6.52 (1H, t, $J$=7.2), 6.44 (1H, dd, $J$=7.1, 0.6), 6.28 (1H, t, $J$=7.6), 5.37 (1H, d, $J$=2.1), 5.08 (1H, q, $J$=2.04, 0.9), 4.61 (2H, s), 2.1 (3H, s); $\delta_C$ ($CDCl_3$, 75.5 MHz): 170.4, 165, 162, 161.4, 136.9, 136.5, 134.8 (t, $^2J_{P-C}$=6), 131.7 (t, $^1J_{P-C}$=23, C–P), 130.0, 129.3, 127.9 (t, $^3J_{P-C}$=5), 127.3, 123.0, 100.6, 87.6, 74.3, 19.8; $\delta_P$ (121.5 MHz): 22.77; FTMS: Exact mass calculated for $C_{49}H_{41}O_3P_2Pd$ 972.08 Found $C_{49}H_{41}O_3P_2Pd$, 846.1588. (The parent peak was not observed.) Crystals suitable for single crystal analysis were prepared by dissolution of **12** in hot $Et_2O$ and subsequent slow cooling between 5 and 8 °C to produce single crystals.

### 5.7. Computational details

Molecular geometries were optimized at the Becke3LYP (B3LYP) level of density functional theory (DFT). The effective core potentials (ECPs) of Hay and Wadt with the double-ζ valence basis sets (LanL2DZ) were used to describe the Pd atom. The 6-311G* Pople basis set was used for those C, H and O atoms involved in the bond breaking and making processes. The standard 6-31G basis set was used for all other atoms. Polarization functions were added for Pd ($\zeta_f$=1.472). Frequency calculations were carried out to confirm the characteristics of all of the optimized structures as minima (zero imaginary frequency) or transition-states (one imaginary frequency) and to provide free energies at 298.15 K, which include entropy contributions. Calculations of intrinsic reaction coordinates (IRC) were also performed to confirm that the transition-states connect two relevant minima. All of the calculations were performed with the Gaussian 03 software package.

DFT calculations (B3LYP) reveal the energy profile of C3/C5 regioselectivity for the formation of six-membered ring products under the reaction conditions (with DMF used as the ligand, *O*-bound). From the energy profile (see overleaf), the pathway leading to C3 regioselectivity was calculated to be more favourable by 6.5 kcal/mol in the free energy barrier. The proton-abstraction step is also easier at C3 (3.3 kcal/mol) than that at C5 (9.0 kcal/mol). Although the barrier for C5 regioselectivity is higher it is still accessible.

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